

## **Appendix 3-C**

### **Levels of Significant Exposure to Lead**

**Source: U.S. Department of Health and Human Services, 1999.  
*Toxicological Profile for Lead.* p. 127.**

Table 2-4. Levels of Significant Exposure to Lead - Oral

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
ACUTE EXPOSURE							
Systemic							
1	Human	5 d 1x/d (C)	Hemato		0.03 M (24-61% decrease in ALAD activity)		Cools et al. 1976  PbAc
2	Human	3-14 d 7 d/wk 1x/d (C)	Hemato		0.02 (decreased ALAD activity)		Stuik 1974  PbAc
3	Rat (Wistar)	once (GW)	Hemato		17.5 F (increased activity of ALA-S in liver and kidney)		Chmielnicka et al. 1994  PbAc
4	Rat (Sprague- Dawley)	10 d ad lib  (W)	Bd Wt		17.5 F (approximately 19% decreased body weight gain)		Minnema and Hammond 1994  PbAc
			Other		17.5 F (approximately 18% and 27% reductions in food and water intake, respectively)		
5	Rat (Fischer- 344)	6 d ad lib (W)	Hemato		146 M (decreased erythrocyte ALAD activity; increase urinary coproporphyrins)		Simmonds et al. 1995  PbAc

Table 2-4. Levels of Significant Exposure to Lead - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	LOAEL		Reference Chemical Form
				NOAEL (mg/kg/day)	Less serious (mg/kg/day)	Serious (mg/kg/day)
6	Rat (Holtzman)	1-2 wk ad lib (F)	Other		734.7 M (blockage of calcium intestinal transport response to vitamin D)	Smith et al. 1981  PbAc
<b>Immunological/Lymphoreticular</b>						
7	Mouse (Swiss- Webster)	14 d 7 d/wk 1x/d (G)			2.6 (decreased spleen and thymus weight, leukopenia)	Hillam and Ozkan 1986  Pb(NO <sub>3</sub> ) <sub>2</sub>
<b>Neurological</b>						
8	Rat (Wistar)	ppd 9-18 1x/d (GW)				50 M (impaired latent learning)  Massaro and Massaro 1987  PbAc
<b>Reproductive</b>						
9	Rat (COBS)	Gd 6-16 11 d 1x/d (GW)		39 F		390 F (decreased number of pregnancies)  Kennedy et al. 1975  PbAc
10	Mouse (CD-1)	Gd 5-15 11 d 1x/d (GW)		39 F		390 F (decreased number of pregnancies)  Kennedy et al. 1975  PbAc
<b>Developmental</b>						
11	Rat (COBS)	Gd 6-16 11 d 1x/d (GW)		39		390 (increased fetal resorptions, retarded skeletal development)  Kennedy et al. 1975  PbAc

Table 2-4. Levels of Significant Exposure to Lead - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
INTERMEDIATE EXPOSURE							
Death							
12	Mouse (HET)	multi gen (W)				605 F (increased fatality rates)	Rasile et al. 1995  PbAc
Systemic							
13	Human	7 wk 7 d/wk 1x/d (C)	Hemato		0.01 M (decrease ALAD activity; increased RBC porphyrin)		Cools et al. 1976  PbAc
14	Human	21 d 7 d/wk 1x/d (C)	Hemato		0.02 (increased protoporphyrin IX in RBC of females)		Stuik 1974  PbAc
15	Monkey (Rhesus)	174 d (2 d at 10 mg/kg, 12 d at 3 mg/kg, 160 d at 0.7 mg/kg) 1x/d (GW)	Hemato  Other	  0.7	0.7 (increased ZPP)		Levin et al. 1988  PbAc
16	Rat (Sprague- Dawley)	6 wk ad lib (W)	Cardio		873 M (myofibrillar fragmentation, mitochondrial swelling)		Asokan 1974  PbAc

Table 2-4. Levels of Significant Exposure to Lead - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
17	Rat (Fischer- 344)	30 d (F)	Hemato	1.5 M	5 M (increased urinary excretion of aminolevulinic acid)		Dieter et al. 1993  PbAc
			Renal	0.5 M	1.5 M (mild to moderate enlargement of nuclei in renal tubules)		
			Bd Wt	1.5 M	5 M (14-20% reduction in weight gain)		
			Other	5 M			
18	Rat (Fischer- 344)	30 d (F)	Hemato	1.5 M	5 M (increased urinary excretion of aminolevulinic acid)		Dieter et al. 1993  PbO
			Renal	1.5 M	5 M (mild to moderate enlargement of nuclei in renal tubules)		
			Bd Wt	1.5 M	5 M (14-20% reduction in weight gain)		
			Other	5 M			

Table 2-4. Levels of Significant Exposure to Lead - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
19	Rat (Fischer- 344)	30 d (F)	Hemato	5 M			Dieter et al. 1993
							PbS
			Renal	5 M			
			Bd Wt	5 M			
20	Rat (Fischer- 344)	30 d (F)	Other	5 M			
			Hemato	5 M			Dieter et al. 1993
							Pb Ore
			Renal	5 M			
21	Rat (Wistar)	50 d (F)	Bd Wt	5 M			
			Other	5 M			
			Musc/skel		1 F (Decreased trabecular bone mass and thickness)		Escribano et al. 1997
							PbAc
			Bd Wt	1 F			

Table 2-4. Levels of Significant Exposure to Lead - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
22	Rat (albino)	4 wk ad lib (W)	Hemato		109 M (decreased ALAD activity and hemoglobin; increased urinary excretion of ALA and increased blood zinc protoporphyrin)		Flora et al. 1993  PbAc
			Hepatic		109 M (increased hepatic lipid peroxidation)		
			Bd Wt		109 M (decreased body weight gain, but not quantitated)		
23	Rat (hooded)	3 wk ad lib (W)	Ocular			0.5 F (rod degeneration)	Fox and Chu  PbAc
24	Rat (hooded)	3 wk ad lib (W)	Ocular			0.5 F (alterations in rod photo-receptors)	Fox and Farber 1988  PbAc
25	Rat (Long- Evans)	21 d Ld 1-21 (W)	Ocular		0.08 F (decreased rod sensitivity and range of dark adaptation)		Fox and Katz  PbAc
26	Rat (hooded)	3 wk ad lib (W)	Ocular		0.5 F (decreased retinal sensitivity, rhodopsin, and rod outer segment length)		Fox and Rubinstein 1989  PbAc

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Table 2-4. Levels of Significant Exposure to Lead - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
27	Rat (Fischer- 344)	44 d ad lib (F)	Hemato		0.9 M (reduction in blood ALAD activity)		Freeman et al. 1996
							PbAc
			Bd Wt	6.4 M			
			Other	6.4 M			
28	Rat (Fischer- 344)	44 d ad lib (F)	Hemato		6.4 M (reduction in blood ALAD activity)		Freeman et al. 1996
							PbS
			Bd Wt	6.4 M			
			Other	6.4 M			
29	Rat (Fischer- 344)	44 d ad lib (F)	Hemato		0.9 M (reduction in blood ALAD activity)		Freeman et al. 1996
							Pb Soil
			Bd Wt	6.4 M			
			Other	6.4 M			
30	Rat (Sprague- Dawley)	1-12 months (W)	Musc/skel		7.5 M (Decreased femur density)		Gruber et al.  PbAc
31	Rat (Long- Evans)	26 d (W)	Musc/skel		145 M (altered bone development)		Hamilton and O'Flaherty 1995
							PbAc
			Bd Wt		145 M (13% reduced weight relative to controls)		
			Other		145 M (decreased food intake)		



Table 2-4. Levels of Significant Exposure to Lead - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
32	Rat (Wistar)	20 d ad lib (W)	Hemato		11.1 M (36% decrease in ALAD activity in erythrocytes on day 20)		Hayashi et al. 1993  PbAc
			Hepatic	11.1 M			
			Renal	11.1 M			
			Bd Wt	11.1 M			
33	Rat (Sprague- Dawley)	63 d ad lib (W)	Hemato	0.9			Hubermont et al. 1976  Pb(NO <sub>3</sub> ) <sub>2</sub>
34	Rat (Long- Evans)	90 d ad lib (W)	Bd Wt	38 M			Kala and Jadhav 1995a  PbAc
			Other	38 M			
35	Rat (NS)	20-30 d 1x/d ad lib (W)	Hepatic	0.005	0.05	(decreased RNA, glycogen; pyknosis of Kupffer cells; increased liver weight)	Krasovskii et al. 1979  PbAc

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Table 2-4. Levels of Significant Exposure to Lead - Oral (continued)

Key to <sup>a</sup> figure	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
36	Rat (NS)	6-12 mo ad lib (W)	Hemato	0.0015	0.005	(impaired heme synthesis assessed by increased excretion of ALA and porphobilinogen)	Krasovskii et al. 1979  PbAc
			Hepatic	0.0015	0.005	(decreased glycogen, RNA, sulfhydryl groups, alterations in activities of oxidizing enzymes)	
37	Rat (Long- Evans)	18 d 1x/d (GW)	Hemato	6.4	19.2	(decreased hematocrit)	Overmann 1977  PbAc
38	Rat (Long- Evans)	159 d ad lib (W)	Cardio	0.03 F	0.3 F	(increased systolic blood pressure)	Perry and Erlanger 1978  PbAc
39	Rat (Sprague- Dawley)	14 - 50 ad lib (W)	Bd Wt			502 M (24% reduction in body weight gain)	Ronis et al. 1996  PbAc
			Other		502	(17-20% reduction in water intake)	

Table 2-4. Levels of Significant Exposure to Lead - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
40	Rat (Fischer- 344)	10 wk ad lib (W)	Hemato		14.6 M (decreased erythrocyte ALAD activity and ZPP/heme ratio; increased urinary coproporphyrins)		Simmonds et al. 1995  PbAc
41	Rat (NS)	20 wk 5 x/wk (GW)	Bd Wt	0.64			Singh 1993  PbAc
			Other	0.64			
42	Rat (Porton)	4 mo 1 x/d (G)	Hepatic		64 F (significant reduction in hepatic AST, ALT and AP activities)		Singh et al. 1994  PbAc
43	Rat (Buffalo)	7 wk 1-2 x/wk (G)	Cardio			5 M (atrophy of the elastic fibers of the aorta)	Skoczynska et al. 1993  PbAc
			Hepatic		5 M (24% increase in serum triglycerides)		
			Bd Wt	20 M			
44	Rat (Wistar)	2-3 mo 7 d/wk ad lib (W)	Renal	414		828 M (proximal tubular dysfunction; increased urinary excretion of B2- microglobulin)	Vyskocil et al. 1989  PbAc

Table 2-4. Levels of Significant Exposure to Lead - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
45	Rat (Wistar)	2-4 mo ad lib (W)	Renal	81 F	320 F (tubular dysfunction as indicated by 2-3-fold increase in urinary excretion of B2-microglobulin)		Vyskocil et al. 1995  PbAc
			Bd Wt	320 F			
			Other	81 F	320 F (water intake reduced by half)		
46	Rat (Wistar)	7-8 wk 7 d/wk (F)	Hemato		318 M (decreased hematocrit)		Walsh and Ryden 1984  PbAc
			Renal		318 M (increased kidney weight)		
			Bd Wt		318 M (18% reduction in body weight gain)		
47	Rat (Wistar)	13 wk ad lib (W)	Bd Wt		77 M (15% reduction in final body weight)		Yokoyama and Araki 1992  PbAc
<b>Immunological/Lymphoreticular</b>							
48	Rat (Fischer- 344)	31 d  (W)		17	42 (decrease in blood total leukocyte count in offspring)		Miller et al. 1998  PbAc

Table 2-4. Levels of Significant Exposure to Lead - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
Neurological							
49	Monkey (Rhesus)	344-362 d 7 d/wk 1x/d (F)				0.3 (deficit in reversal learning during exposure and 3 years after exposure ceased)	Bushnell and Bowman 1979b  PbAc
50	Monkey (Rhesus)	357 d (2 d at 10mg/kg, 12 d at 3 mg/kg, 343 d at 0.7 mg/kg) 1x/d (G)				0.7-10 (impaired open field behavior, behavioral alterations)	Ferguson and Bowman 1990  PbAc
51	Monkey (Cynomolgus)	200 d 5 d/wk 1x/d (GW)		0.05		0.1 (impaired spatial discrimination reversal task at 9-10 years of age)	Gilbert and Rice 1987  PbAc
52	Monkey (Rhesus)	174 d (2 d at 10 mg/kg, 12 d at 3 mg/kg, 160 d at 0.7 mg/kg) 1x/d (GW)			0.7-10 (lower muscle tonus; decreased visual attentiveness)		Levin et al. 1988  PbAc
53	Monkey	200 d 5 d/wk 1x/d (GW)			0.05 (impaired nonspatial discrimination at 3 years of age)		Rice 1985b  PbAc

Table 2-4. Levels of Significant Exposure to Lead - Oral (continued)

Key to <sup>a</sup> figure	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
54	Rat (NS)	35 d ad lib (W)			1.6 M (reduced radial maze accuracy)		Bushnell and Levin 1983  PbAc
55	Rat (Long- Evans)	>50 d ad lib (W)			4.2 M (increased sensitivity to muscarinic cholinergic agonists)		Cory-Slechta and Pokora 1995  PbAc
56	Rat (Wistar)	335 d ad lib (W)			9.5 M (increased fixed interval response rates to lever press)		Cory-Slechta et al. 1983  PbAc
57	Rat (Long- Evans)	186 d ad lib (W)			2.1 M (higher response rate for operant learning tests)		Cory-Slechta et al. 1985  PbAc
58	Rat (Long- Evans)	21 d (W)			8.3 (increased sensitivity of D2-D3 receptor subtype to dopamine agonists)		Cory-Slechta et al. 1992  PbAc
59	Rat (Long- Evans)	90 d ad lib (W)			2.2 M (reduction in dopamine in nucleus accumbens and in serotonin in brain stem and frontal cortex)		Kala and Jadhav 1995a  PbAc

Table 2-4. Levels of Significant Exposure to Lead - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
60	Rat (Long- Evans)	90 d ad lib (W)			4 M (reduced basal and potassium induced release of dopamine from the nucleus accumbens)		Kala and Jadhav 1995b  PbAc
61	Rat (NS)	6-12 mo ad lib (W)		0.0015	0.005 (disruption of conditioned responses and motor activity)		Krasovskii et al. 1979  PbAc
62	Rat (Wistar)	112 d ad lib (W)		14.3 M			Massaro and Massaro 1987  PbAc
63	Rat (Long- Evans)	18 d 1 x/d (GW)		6.4		19.2 (increased motor activity and operant delayed response; impaired motor coordination)	Overmann 1977  PbAc
64	Rat (NS)	20 wk 5 x/wk (GW)			0.64 (altered normal developmental pattern of proteins in neurons of young exposed prenatally and continued postnatally)		Singh 1993  PbAc

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Table 2-4. Levels of Significant Exposure to Lead - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
65	Rat (NS)	10 wk 5 d/wk 1x/d (G)			0.64	(altered levels of neurotransmitters in the brain after pre- and postnatal exposure)	Singh and Ashraf 1989  PbAc
66	Rat (NS)	10 wk 5 d/wk 1x/d (G)		0.64			Singh and Ashraf 1989  PbAc
67	Rat (Long- Evans)	21 d (W)			8.3	(increased number of D2 dopaminergic receptors in striatum and nucleus accumbens)	Widzowski et al. 1994  PbAc
68	Rat (Wistar)	15 wk ad lib (W)			89.6 M	(decrease in motor nerve conduction velocity)	Yokoyama and Araki 1986  PbAc
69	Rat (Wistar)	13 wk ad lib (W)			77 M	(decreased slow axonal transport of proteins)	Yokoyama and Araki 1992  PbAc
<b>Reproductive</b>							
70	Rat (Wistar)	9 wk 7 d/wk 1x/d (GW)			0.19 M	(decreased number of spermatozoa)	Barratt et al. 1989  PbAc



Table 2-4. Levels of Significant Exposure to Lead - Oral (continued)

Key to <sup>a</sup> figure	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
71	Rat (albino)	60 d ad lib (W)		22 M	45 M (partial inhibition of spermatogenesis)	90 M (testicular atrophy, cellular degeneration)	Chowdhury et al. 1984  PbAc
72	Rat (NS)	312 d 7 d/wk ad lib (W)		34			Fowler et al. 1980  PbAc
73	Rat (NS)	30 d 1x/d (G)			0.013 M (increased prostate weight)	0.26 M (impotence; hyperplasia; increase prostate weight)	Hilderbrand et al. 1973  PbAc
					0.014 F (irregular estrus cycles)	0.28 F (ovarian cysts; persistent vaginal estrus)	
74	Rat (Sprague- Dawley)	63 d ad lib (W)		0.9 F			Hubermont et al. 1976  Pb(NO <sub>3</sub> ) <sub>2</sub>
75	Rat (NS)	6-12 mo ad lib (W)		0.0015 M	0.05 M (decreased activity of AIDH, SDH, NAD, and NADPH-diaphorase in spermatogenic epithelium and swelling of follicular epithelial cells in males)		Krasovskii et al. 1979  PbAc
76	Rat (NS)	20-30 d ad lib (W)		0.0015	0.005 M (dystrophy of Leydig cells)	0.05 M (decreased motility of spermatozoa, acid phosphatase activity increased)	Krasovskii et al. 1979  PbAc

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Table 2-4. Levels of Significant Exposure to Lead - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
77	Rat (Sprague- Dawley)	14 - 50 ad lib (W)				502 (decreased testicular weights; delayed vaginal opening and disruption of estrus cycling)	Ronis et al. 1996  PbAc
78	Rat (Sprague- Dawley)	Gd 5-21 PNd 21-85 ad lib (W)			42 (reduced plasma testosterone and 17B-estradiol at birth)		Ronis et al. 1998b, 1998c  PbAc
79	Rat	30 d ad lib (W)			40 (decreased LH and prolactin levels)		Sourgens et al. 1987  PbAc
80	Mouse (NMRI)	12 wk 7 d/wk 1x/d (W)				141 M (decreased number of implantations)	Johansson and Wide 1986  PbCl <sub>2</sub>
81	Mouse (NMRI)	6 wk ad lib (W)		176 F			Kristensen et al. 1995  PbCl <sub>2</sub>
<b>Developmental</b>							
82	Monkey (Rhesus)	Gd 1-165 165 d (W)		5.7			Bushnell and Bowmann 1979a  PbAc

Table 2-4. Levels of Significant Exposure to Lead - Oral (continued)

Key to <sup>a</sup> figure	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	LOAEL			Reference Chemical Form
				NOAEL (mg/kg/day)	Less serious (mg/kg/day)	Serious (mg/kg/day)	
83	Monkey ( <i>Macaca fascicularis</i> )	Gd 1-165 195-210 d 1x/d (GW)				3 F (deficit in form discrimination at 6-18 months and in response to inhibition at 19-29 months in offspring)	Hopper et al. 1986  Pb(NO <sub>3</sub> ) <sub>2</sub>
84	Monkey (Rhesus)	Gd 1-165 8.5 mo ad lib (W)		3.8			Levin and Bowman 1983  PbAc
85	Rat (Sprague-Dawley)	34 d Gd 16-21 PND 1-28 ad lib (W)				166 (30-40% reduction in ChAT activity in septum and hippocampus from pups and 30-40% decrease in cholinergic muscarinic receptors in septum)	Bielarczyk et al. 1994  PbAc
86	Rat (CD)	56 d ad lib (W)			25 (delayed synthesis of cytochrome C in cerebral cortex in male pups neonatally exposed)		Bull et al. 1979  PbCl <sub>2</sub>
87	Rat (Sprague-Dawley)	Gd 1-21 105-115 d ad lib (W)				3.5 (suppression of delayed hyper-sensitivity response and lymphocyte responsiveness to mitogen stimulation; decreased thymic weight in pups)	Faith et al. 1979  PbAc

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Table 2-4. Levels of Significant Exposure to Lead - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
88	Rat (NS)	Gd 1-21 312 d ad lib (W)		0.07	0.7 (elevated kidney weight, cytomegaly in male pups)		Fowler et al. 1980  PbAc
89	Rat (CD)	201-291 d ad lib (W)		0.7	3.5 (delays in vaginal opening in pups)	7 (delayed righting reflex in pups)	Grant et al. 1980  PbAc
90	Rat (Sprague- Dawley)	70 d (W)			38 (decreased body weight and tail length in pups)		Hamilton and O'Flaherty 1994  PbAc
91	Rat (Wistar)	Gd 1-21 ad lib (W)			0.45 (decreased erythrocyte ALAD activity in pups; lower fetal weights)		Hayashi 1983  PbAc
92	Rat (Sprague- Dawley)	63 d ad lib (W)		0.09	0.9 (decreased ALAD activity, increased protoporphyrins in pups)		Hubermont et al. 1976  Pb(NO <sub>3</sub> ) <sub>2</sub>
93	Rat (CD)	84-91 d ad lib (W)		0.7	3.5 (delayed vaginal opening)		Kimmel et al. 1980  PbAc
94	Rat (Sprague- Dawley)	Gd 1-21 105-112 d 1x/d (W)				2.24 (immune suppression; decreased thymus weight in pups)	Luster et al. 1978  PbAc

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Table 2-4. Levels of Significant Exposure to Lead - Oral (continued)

Key to <sup>a</sup> figure	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
95	Rat (CD)	56 d ad lib (W)				28 (delayed cortical development in pups)	McCauley et al. 1979  PbCl2
96	Rat (Long- Evans)	Gd 1-21 41 d 1x/d (GW)		48	64 (decreased fetal weight)		Miller et al. 1982  PbAc
97	Rat (Sprague- Dawley)	138-145d two gen (W)				0.7 (impaired righting reflex in pups)	Reiter et al. 1975  PbAc
98	Rat (Wistar)	77 d mat gest lact ad lib (W)		18	36 (increased activity in open field; failure to habituate to environment)		Rodrigues et al. 1993  PbAc
99	Rat (Wistar)	94 d mat gest lact ad lib (W)			17.5 (increased relative kidney weight in 6-month-old rats; increased ALAD reactivation index in kidney from 6-month-old rats)		Rodrigues et al. 1996  PbAc

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Table 2-4. Levels of Significant Exposure to Lead - Oral (continued)

Key to <sup>a</sup> figure	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	LOAEL		Reference Chemical Form	
				NOAEL (mg/kg/day)	Less serious (mg/kg/day)		Serious (mg/kg/day)
100	Rat (Sprague- Dawley)	Gd 5-21 Ld 1-21 Pd 21-85 ad lib (W)				502 (19% incidence of stillbirth vs 2% in controls; reduced weight gain of pups; decreased serum testosterone)	Ronis et al. 1996  PbAc
101	Rat (Sprague- Dawley)	Gd 5-21 PNd 21-85 ad lib (W)		42	126 M (reduced birth weight, crown-to-rump length, and anogenital distance)	377 (28% rate of stillbirth compared to 4% in controls)	Ronis et al. 1998b, 1998c  PbAc
102	Rat (Wistar)	3 wk 7 d/wk ad lib (W)				15 (increase in volume of mossy fiber zone, granule cell layer, and commissural association zone in hippocampus of offspring)	Slomianka et al. 1989  PbAc
103	Rat (Sprague- Dawley)	Gd 1-21 56 d ad lib (W)				28 (slower extinction of acquired response when reward not present relative to controls)	Taylor et al. 1982  PbAc
104	Rat (Charles River)	Gd 1-21 5 mo (W)			2.2 (inhibit renin synthesis and release)		Victory et al. 1982a  PbAc

2. HEALTH EFFECTS

Table 2-4. Levels of Significant Exposure to Lead - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
105	Mouse (HET)	Gd 1-21 41 d ad lib (W)				608 (altered measures of square crossing and standups in open field, and in time to return to home cage)	Draski et al. 1989  PbAc
106	Gn Pig (NS)	Gd 22-52 Gd 22-62  (GW)				5.5 (reduced levels of gonadotropin-releasing hormone and somatostatin in hypothalamus from 52- and 62-day-old fetuses)	Sierra and Tiffany- Castiglioni 1992 PbAc
107	Gn pig (NS)	Gd 22 to Gd 52 or Gd 62 1x/d (GW)				5.5 (decrease in the neuroglial enzymes GPDH and glutamine synthetase, decreased blood ALAD and increased ZPP levels in pups and dams)	Sierra et al. 1989  PbAc

**CHRONIC EXPOSURE****Systemic**

108	Monkey (Rhesus)	9 yr (F)	Ocular		4 (decrease tyrosine hydroxylase in retinal cells; indication of alterations in cell wiring)		Kohler et al. 1997  PbAc
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Table 2-4. Levels of Significant Exposure to Lead - Oral (continued)

Key to <sup>a</sup> figure	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
109	Monkey (Rhesus)	1 yr 7 d/wk 1x/d (F)	Hemato	0.57			Mele et al. 1984
			Bd Wt	0.57			PbAc
110	Monkey (Macaca fascicularis)	19-14 yr (C)	Hemato	2			Rice 1996
			Bd Wt	2			PbAc
111	Rat (NS)	2 yr ad lib (F)	Hemato	0.9	3.1 (decreased ALAD activity)		Azar et al. 1973
			Bd Wt	27	56.5 (unspecified decrease in weight gain)		PbAc
112	Rat (Sprague- Dawley)	18 mo 7 d/wk 1x/d (W)	Cardio	1.4 M	2.8 M (increased systolic and diastolic blood pressure)		Carmignani et al. 1988a
			Hepatic	5.6 M			PbAc
			Renal	5.6 M			
113	Rat (Sprague- Dawley)	76 wk ad lib (W)	Renal			371 M (necrotic & dilated cortical tubules, tubular protein casts)	Koller et al. 1985  PbAc

2. HEALTH EFFECTS



Table 2-4. Levels of Significant Exposure to Lead - Oral (continued)

Key to <sup>a</sup> figure	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
114 Rat (Long- Evans)		<18 mo 7 d/wk 1x/d (W)	Cardio		0.014 F (increase in systolic blood pressure)		Perry et al. 1988
			Bd Wt	0.71 F			PbAc
115 Dog (Beagle)		2 yr ad lib (F)	Hemato	1.25	2.5 (decreased ALAD activity)		Azar et al. 1973
			Renal	2.5	12.5 (cytomegaly in males)		PbAc
			Bd Wt	12.5			
<b>Neurological</b>							
116 Monkey (Rhesus)		365 d (G)		0.7			Ferguson et al. 1996
							PbAc
117 Monkey (Rhesus)		1 yr 7 d/wk 1x/d (F)				0.21 (reversal learning deficit; electrophysiological changes in auditory process)	Laughlin et al. 1983
							PbAc
118 Monkey (Rhesus)		1 yr 7 d/wk ad lib (F)		0.64			Levin and Bowman 1989
							PbAc
119 Monkey (Rhesus)		gestation to 9.75 yr (F)			4 (increased wave latency of brain stem auditory evoked potentials)		Lilienthal and Winneke 1996
							PbAc

Table 2-4. Levels of Significant Exposure to Lead - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
120	Monkey (Rhesus)	1 yr 7 d/wk 1x/d (F)			0.19 (deficit in fixed interval schedule)		Mele et al. 1984  PbAc
121	Monkey (Rhesus)	9 yr (F)			7 (decrease content of S100 protein in hippocampal glia cells)		Noack et al. 1996  PbAc
122	Monkey (Cynomolgus)	200-270 d 7 d/wk 1x/d (G)				0.05 (impaired operant learning)	Rice 1985b  PbAc
123	Monkey (Rhesus)	7-8 yr 1 x/d (C)				1.5 (altered performance on a fixed-interval-fixed-ratio schedule of reinforcement at age 7-8 years)	Rice 1992  PbAc
124	Monkey (Macaca fascicularis)	13 yr (C)			2 (increased pure tone hearing thresholds)		Rice 1997  PbAc
125	Monkey (Macaca fascicularis)	15-18 yr (F)			0.5 (slight increase in vibration threshold)		Rice and Gilbert 1995  PbAc
126	Monkey (Macaca fascicularis)	7-8 yr 5 d/wk 1x/d (C)				0.05 (impairment in delayed alternation behavioral task)	Rice and Karpinski 1988  PbAc

2. HEALTH EFFECTS

Table 2-4. Levels of Significant Exposure to Lead - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
127	Dog (Beagle)	2 yr 7 d/wk ad lib (F)		12.5			Azar et al. 1973  PbAc
<b>Reproductive</b>							
128	Monkey (Cynomolgus)	10 yr 1 x/d  (C)			1 F (decreased serum level of luteinizing and follicle stimulating hormones, and estradiol)		Foster 1992  PbAc
129	Monkey (Cynomolgus)	10 yr 1 x/d  (C)			1 M (disrupture of general architecture of seminiferous epithelium)		Foster et al. 1998  PbAc
130	Monkey (Rhesus)	75 mo 5 d/wk (W)			1.3 F (impaired menstrual cycle)		Franks et al.  PbAc
<b>Cancer</b>							
131	Rat (NS)	2 yr 7 d/wk ad lib (F)				27 (CEL: 5/50 renal tubular adenomas in males)	Azar et al. 1973  PbAc
132	Rat (Sprague- Dawley)	76 wk ad lib (W)				371 M (CEL: renal tubular carcinomas in 13/16)	Koller et al. 1985  PbAc

Table 2-4. Levels of Significant Exposure to Lead - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
133	Mouse (Swiss)	2 yr ad lib (F)				83.2 (CEL: renal tubular adenomas and carcinomas in 7/25)	Van Esch and Kroes 1969  PbAc

<sup>a</sup>The number corresponds to entries in Figure 2-2.

ad lib = ad libitum; ALA = aminolevulinic acid; ALAD = aminolevulinic acid dehydratase; ALA-S = delta-aminolevulinic acid synthetase; ALT = alanine aminotransferase; AP = alkaline phosphatase; AST = aspartate aminotransferase; Bd Wt = body weight; (C) = capsule; Cardio = cardiovascular; CEL = cancer effect level; ChAT = choline acetyltransferase; d = day(s); F = female; (F) = food; (G) = gavage; Gd = gestational day; gen = generation; GPDH = glucose-6-phosphate dehydrogenase; (GW) = gavage in water; Hemato = hematological; lact = lactation; Ld = lactational day; LD<sub>50</sub> = lethal dose, 50% kill; LH = luteinizing hormone; LOAEL = lowest-observable-adverse-effect level; M = male; mat gest = mating gestation; mo = month(s); multi gen = multigenerational; NOAEL = no-observable-adverse-effect level; NS = not specified; Pd = postnatal day; RBC = red blood cell; RNA = ribonucleic acid; (W) = water; wk = week(s); yr = year(s); x = times; ZPP = zinc protoporphyrin